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PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 4 :		(11) International Publication Number: WO 88/ 10110
A61K 7/18, 9/46, 33/16	A1	(43) International Publication Date: 29 December 1988 (29.12.88)

(21) International Application Number: PCT/US88/02098

(22) International Filing Date: 22 June 1988 (22.06.88)

(31) Priority Application Number: 066,831

(32) Priority Date: 25 June 1987 (25.06.87)

(33) Priority Country: US

(71) Applicant: DENTAB, INC. [US/US]; 26 Strawberry Hill Avenue, Stamford, CT 06902 (US).

(72) Inventors: ABERG, Torwald ; Tradgardsvagen 11C, S-181 62 Lidingo (US). STURTON, Julian, D. ; 528 East 85th Street, Apt. 2A, New York, NY 10028 (US).

(74) Agent: DAVIS, F., Eugene, IV; Law Offices of F. Eugene Davis IV, 184 Atlantic Street, Stamford, CT 06901 (US).

(81) Designated States: AT, AT (European patent), AU, BB, BE (European patent), BG, BJ (OAPI patent), BR, CF (OAPI patent), CG (OAPI patent), CH, CH (European patent), CM (OAPI patent), DE, DE (European patent), DK, FI, FR (European patent), GA (OAPI patent), GB, GB (European patent), HU, IT (European patent), JP, KP, KR, LK, LU, LU (European patent), MC, MG, ML (OAPI patent), MR (OAPI patent), MW, NL, NL (European patent), NO, RO, SD, SE, SE (European patent), SN (OAPI patent), SU, TD (OAPI patent), TG (OAPI patent).

Published
With international search report.

(54) Title: A TOOTH CLEANING AND FLUORIDATING TABLET

(57) Abstract

The substantially water free tablet when chewed in the mouth forms a self-foaming paste containing stannous fluoride. The tablet contains less than about 50 % by weight of a composition producing carbon dioxide when mixed with the saliva in the mouth, and greater than about 35 % by weight of a substantially insoluble filling and polishing composition, and a wetting and foam stabilizing composition which forms the paste. Preferably the filling and polishing composition comprises greater than about 50 % of said tablet and said carbon dioxide producing composition comprises less than about 25 % by weight of said tablet. The tablet is water free to prevent degradation of the stannous fluoride before use. A tablet is chewed to form the paste. The paste is swished around in the mouth and between the teeth to perform a mechanical cleaning action and to bring the stannous fluoride in contact with the tooth surfaces. The tablet is then swallowed. Twice a day use provides an anti-caries and anti-plaque effect greater than that heretofore achieved by any dental hygiene product.

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A TOOTH CLEANING AND FLUORIDATING TABLET

RELATED APPLICATIONS

This application is a continuation-in-part of U.S. Patent Application Serial No. 928,571, filed November 10, 1986, by Torwald Aberg, entitled A TOOTH CLEANING TABLET, which was a continuation of U.S. Patent Application Serial No. 765,158, filed August 13, 1985, by Torwald Aberg, entitled A TOOTH CLEANING TABLET, which claimed priority from United Kingdom application Serial No. 8421226, filed August 21, 1984. Said applications are incorporated herein by reference.

TECHNICAL FIELD

This invention relates to dental hygiene and more particularly to chewable tablets for improving dental hygiene.

BACKGROUND ART

Various dental hygiene tablets are found in the prior art. Westlake, U.S. Patent No. 1,262,888 discloses a tablet comprised of tartaric and citric acid, sodium bicarbonate and desiccated fruit pulp which dissolves with effervescence in the mouth into a thin slurry. The tablet may also "sparingly" incorporate "precipitated chalk to reinforce the desiccated pulp". Howell, U.S. Patent No. 3,962,417 discloses an effervescent dentifrice in chewable tablet form, again employing a high percentage of a carbon dioxide producing couple, namely 68% by weight, magnesium carbonate 11%, and stannous fluoride. Emond, U.S. Patent No. 3,116,208 discloses a dental cleanser in tablet form comprised of calcium carbonate and sodium lauryl sulphate. According to the patent this mixture will foam upon brushing. Gyarmathy et al, U.S. Patent No. 3,432,339 discloses a tablet dentifrice. This tablet comprises a high proportion of substantially insoluble polishing agents 66%, 10% wax, 5½% Floc (finely divided woodpulp cellulose), stannous fluoride, and 2% of hydrogenated coco fatty acid monoglyceride sulfate, a detergent. Sproul, British Patent No. 1,259,342 discloses a dentifrice tablet which is either placed on the toothbrush or in the mouth, with or without water, to form a standard toothpaste. Barels et al, U.S. Patent No. 4,411,885 discloses a tablet to dentifrice employing a surfactant, that is, a detergent, for sudsing.

Thus, the prior art can be categorized as disclosing self-effervescent, that is, CO_2 producing tablets, containing a major portion of CO_2 couple and a minor proportion of polishing agents; these tablets being designed to rapidly dissolve in the mouth to form a liquid or at best a thin slurry. The other prior art tablets are not effervescent, merely tabletted toothpaste, which contains sodium lauryl sulfate, a foam stabilizing agent, which will stabilize any foam formed upon brushing, or a detergent to aid in foaming or sudsing, during brushing or by sucking air into the mouth as proposed by Gyarmathy et al. Recently issued Gioffre et

al U.S. Patent No. 4,627,972 proposed the use of zeolites having adsorbed carbon dioxide to produce the carbon dioxide upon wetting in the mouth for dentifrices and suggests that they may be used in chewable dental tablets.

DISCLOSURE OF THE INVENTION

We have discovered that the use of stannous fluoride as the fluoride agent in a tooth cleaning tablet according to the above-identified Aberg U.S. Patent Applications provides a surprising degree of anti-caries and anti-plaque activities, such as when used twice a day and swallowed will provide the user with the fluoride protection against caries and plaque greater than can be achieved with any prior dental hygiene product.

The tooth cleaning tablet of the invention is designed to form a self-foaming paste when chewed in the mouth. The paste is then swished around the mouth and through the teeth for about 1 to 2 minutes (preferably at least 2 minutes) and then swallowed. This cleans and polishes the tooth surfaces by mechanical action and brings the fluoride and tin ions into contact with the tooth surfaces and the bacterium in the mouth. The fluoride ion in the mouth penetrates the enamel and the tin ion becomes incorporated into the plaque and caries bacteria and has a bacteriostatic action. The swallowed fluoride ion becomes incorporated into newly formed tooth enamel.

In order to provide a paste rather than a thin slurry, which would not be as effective mechanically cleaning or delivering the fluoride and tin ions to the tooth surfaces, we employ less than about 50% by weight of a composition producing carbon dioxide and greater than about 35% by weight of a substantially insoluble filling and polishing composition which forms a paste on chewing in the mouth. Preferably we provide a filling and polishing composition which comprises greater than about 50% by weight of the tablet and a carbon dioxide producing composition comprising less than about 25% by weight of the tablet to prevent excess foaming which would excessively thin the paste. The filling and polishing composition is preferably substantially insoluble in the mouth when the tablet is used and may

contain about 34% polishing agent and about 31% filling agent. The tablet may contain 13% sodium carbonate and 5% acid.

The tablets are substantially water free to prevent degradation of the stannous fluoride and the stannous fluoride is employed in an effective amount, preferably less than about 3% of the tablet.

Use of a tablet containing less than ½% stannous fluoride twice a day provides greater anti-caries and anti-plaque activity than existing dental products as normally used. 1% is probably the upper limit so as to limit the ingestion of fluoride ion to acceptable levels in a 600 milligram tablet. Smaller tablets could have the same amount of fluoride ion at proportionally higher concentrations.

OBJECTS OF THE INVENTION

The object of the invention is to provide a tooth cleaning, caries and plaque reducing tablet for use in the mouth and a method of using the tablet.

Another object of the invention is to provide such a tablet which provides improved anti-caries and anti-plaque activity than heretofore achieved.

Other objects of the invention will in part be obvious and will in part appear hereinafter. The invention accordingly comprises an article of manufacture possessing the features, properties and the relation of elements, a composition of matter possessing the characteristics, properties and the relation of components and a method of using the article and composition, all of which will be exemplified in the articles, compositions, and methods hereinafter described. The scope of the invention will be indicated in the claims.

BEST MODE FOR CARRYING OUT THE INVENTION

The tablet of the invention preferably comprises:

(i) a polishing agent
(ii) a swelling agent
(iii) a foaming agent
(iv) a filling agent
(v) a taste-giving agent
(vi) a wetting agent
(vii) a lubricative agent
(viii) a glidant, and
(ix) a tooth protecting agent, preferably stannous fluoride.

The polishing agent should be substantially insoluable in the mouth and may be an appropriate phosphate, a carbonate or silica, such as pyrogenic silica.

The phosphate may be a metal phosphate. Typical metal phosphates are sodium metaphosphate, potassium metaphosphate, calcium pyrophosphate, magnesium orthophosphate, trimagnesium phosphate, tricalcium phosphate and dicalcium phosphate.

The swelling agent may be sodiumcarboxymethylcellulose, irish moss, tragacanth gum, accacia gum, gelatin, an alginic compound, methylcellulose polyvinylpyrrolidone, xanthan gum or the like.

The alginic compound may be an alginic acid, an alginic salt, or an alginic ester.

The tooth cleaning tablet may contain more than one foaming agent if desired.

The carbon dioxide foaming agent preferably comprises a carbon dioxide source selected from the group consisting of sodium bicarbonate, calcium bicarbonate and potassium bicarbonate and an acid selected from the group consisting of citric acid, tartaric acid, algeric acid and malic acid. However, gas (preferably carbon dioxide) adsorbing agents such as zeolites may be employed.

The filling agent may be a waxy polyethylene glycol such as, for example, that known as carbowax 6000 or carbowax 4000.

The filling agent may alternatively be a hexitol component such as, for example, mannitol or sorbitol or other sugars such as sucrose, xylitol, and fructose.

Still further, the filling agent may be lactat, starch, a silicon oxide, floc or microcrystalline cellulose.

Note that the polishing agents also act as fillers.

The tooth cleaning tablet may contain more than one taste-giving agent if desired. Any taste-giving agent may be employed.

Preferable, the taste-giving agent comprises an aroma giving agent such as menthol, peppermint and spearmint, and a sweetner, either a sugar such as sucrose, mannitol, sorbitol, xylitol or fructose or a synthetic agent such as saccharin, cyclamate or aspertame.

Note that these agents may also act as fillers. The sugars may also act as polishing agents.

The wetting agent may be an oxyethylenoxypropylene polymer, a polyoxyethylensorbitan derivative from a fatty acid, or sodium laurylsulphate. The derivative from the fatty acid may be polyoxyethylensorbitanstearate. A presently preferred wetting agent is sodium laurylsulphate.

The lubricative agent (lubricant) may be magnesium stearate, calcium stearate, stearic acor, or hydrogenated vegetable oil such as Sterotex^{R}, Lubritab^{R}, and Comptritol^{R}.

The tooth cleaning tablet may also contain a plaque indicating agent.

The tooth cleaning tablet preferably contains a tooth protective agent which acts to reduce tooth decay. Usually, the tooth protective agent will improve the resistance of the teeth to attach by acids. The tooth protective agent may also kill plaque producing germs. The tooth protective agent may be sodium fluoride, sodium tetrapyrophosphate, sodium monofluorophosphate, stannous fluoride, a chlorhexidine salt or hexachlorophene. The sodium fluoride may be used in amounts up to 0.3% by volume of the tablet. The

sodium monofluorophosphate may be used in amounts up to 1% by volume of the tablet. Stannous fluoride is preferred.

The formula for the effervescent tablet with the addition of a pyrogenic silica glidant according to the above identified Aberg applications is shown in the accompanying table (F-1). This formula exhibited somewhat poor flow characteristics and a slight degree of sticking. Tablet weight was held at 620 mg (Table I).

Slight modifications were made in the formula to improve flow and lubrication. The milled tribasic calcium phosphate was mixed with an equal portion of unmilled TCP. The lubricant system was changed from 2% magnesium stearate to a mixture of 1% magnesium stearate + 2% stearic acid. Concentration of the Cab-O-Sil^{R} silica glidant was reduced to 0.25%. Formula F-2 was slightly less compressible than F-1 (Table I) but flowed better and caused fewer lubrication problems. Nutrasweet^{R} concentration was doubled and sodium lauryl sulphate reduced to ½.

Prototype tablets (A,B,C) were prepared at 3 hardnesses for evaluation (see below). Tablets were made with stannous fluoride in place of sodium fluoride (.452%). This slight change in quantity was adjusted by slightly lowering the amount of tribasic calcium phosphate. This formula is labeled F-3 (Batch 87103). The concentrations of sodium lauryl sulphate and Nutrasweet^{R} were returned to their original values, 1.61% and .4% respectively.

A product identical to F-3, but containing no stannous fluoride (with slight adjustments in tribasic calcium phosphate) was also prepared for study at three compression forces (A,B,C). This is labeled F-4 (Control Batch 87104) (Table II).

A blend of powders were prepared for feeding studies with three different flavors. Approximately 22 grams of each formulation was blended. Formulas contained stannous fluoride and milled tribasic calcium phosphate. Other blends of powders without test animal unpalatable ingredients (sodium lauryl sulphate, etc.) were also prepared with various flavors.

An attempt was made to modify the original formula to improve both tabletting and taste properties. These changes are shown in Table IV. The level of Nutrasweet^{R} and flavor were reduced slightly, so that they fell somewhere between the original formula and the modified formula. Tablets containing peppermint (Batch 87101) (F-5) and a peppermint/citrus (Batch 87102) (F-6) were prepared for concept testing.

TABLE I

FORMULATIONS OF EFFERVESCENT DENTAL TABLETS

SODIUM FLUORIDE

Ingredient	% w/w F-1 (%)	F-2 (%)	
Tricalcium Phosphate			
Milled	32.26	15.65	31.3
Tritab	0.0	15.65	
Xanthan Gum (Type 200)	8.065	8.065	
Sodium Bicarbonate	12.1	12.1	
Citric Acid	4.84	4.84	
Cab-O-Sil	0.5	0.25	
Xylitol	5.5	5.5	
Nutrasweet	0.4	0.8	
Sodium Lauryl Sulfate	1.61	0.8	
Lubricant			
Mg. Stearate	2.00	1.00	
Stearic Acid	0.0	2.00	
Sorbitol	30.65	30.65	
Sodium Fluoride	0.2419	0.2419	
Spearmint Flavor	1.84	2.5	

TABLE II

FORMULATION OF EFFERVESCENT DENTAL TABLETS
Stannous Flouride

	% w/w	
	F-3 Batch 87103 (%)	F-4 Control Batch 87104 (%)
Ingredient		
Tri. Cal. Phos.	(31.29)	(31.74)
-Milled	15.645	15.87
-Tritab	15.645	15.87
Xanthan Gum 200	8.065	8.065
$NaHCO_3$	12.1	12.1
Citric Acid Anhydrous	4.84	4.84
Cab-O-Sil	0.25	0.25
Xylitol	5.5	5.5
Nutra Sweet	0.4	0.4
SLS	1.61	1.61
Lubricant		
-Mg. Stearate	1.00	1.00
-Stearic Acid	2.00	2.00
Sorbitol	30.65	30.65
Stannous Fluoride	0.452	0.00
Spearmint Flavor	1.84	1.84

Hardness

	F-3% Batch 87103 Newtons	F-4 Control Batch 87104 Newtons
A	20-22	20-22
B	40-45	40-45
C	60-65	60-65

Weight per tablet = 620 mg.

TABLE III

FEEDING STUDY FORMULATION
Dental Powder

	% w/w	
	%	g
Tri Cal.Phos (milled)	31.9	7.018
Xanthan Gum - 200	8.065	1.773
$NaH\ CO_3$	12.1	2.662
Citric Acid	4.84	1.065
Cab-O-Sil	0.25	0.055
Xylitol	5.5	1.21
Saccharin Sodium	0.2	0.044
Sodium Lauryl Sulfate	0.8	0.176
Mg. Stearate	1	0.22
Stearic Acid	2	0.44
Sorbitol	30.65	6.743
NaF	0.2419	0.053
Flavor (A,B,C)	2.5	0.55
		22.00g

Flavor A Art. milk chocolate flavor
B Art. cheddar cheese flavor
C Art. bacon flavor

TABLE IV

CHANGES IN MODIFIED FORMULA TO IMPROVE TASTE

	Modified Formulas F-2	Batch 87101 F-5	% w/w Batch 87102 F-6
Tri. Cal. Phos.	(31.3)	(31.79)	(31.79)
-Milled	15.65	15.9	15.9
-Tritab	15.65	15.9	15.9
Cab-O-Sil	0.25	0.25	0.25
Nutra Sweet	0.8	0.6	0.6
SLS	0.8	0.8	0.8
Lubricant			
-Mg. Stearate	1.00	1.00	1.00
-Stearic Acid	2.00	2.00	2.00
Flavor			
Spearmint	2.5	--	--
Peppermint	--	2.2	--
Peppermint/Citrus	--	--	2.2

LIST OF INGREDIENTS

Material	Lot. No.	Suppliers
Tricalcium Phosphate Milled - NF Grade	Product No. 058810	Stauffer Chemical Co. Westport, CT 06881
Unmilled-Tritab NF	Lot 7213	Stauffer Chemical Co. Westport, CT 06881
Xanthan Gum 200 (Rhodigel-200)	860030-1	R.T. Vanderbilt Co., Inc Norwalk, CT 06855
Sodium Bicarbonate USP Powder	H20485J13	Amend Drug & Chemical Co. Irvington, NJ 07111
Citric Acid, Anhydrous Powder	732-8160	J.T. Baker Chemical Co. Phillipsburg, NJ 08865
Cab-O-Sil, Grade S-17	IBI30	Cabot Corp. Boston, MA 02110
Xylitol		
Nutrasweet	U60217	Searle Food Resources Inc. Skokie, IL 60076
Sodium Lauryl Sulfate USP	Lot 110-101	Ruger Chemical Co., Inc. Long Island City, NY
Lubricant Magnesium Stearate Stearic Acid	Lot 2255P15	Mallinckrodt Co. St. Louis, Mo 63147

Material	Lot. No.	Suppliers
Sorbitol, NF Crystalline Coarse Powder	G33081-S6926	Pfizer Chemical Division New York, NY 10017
Sodium Flouride, USP Powder	J23449P17	Amend Drug & Chemical Co. Irvington, NJ 07111
Stannous Flouride, Anhydrous	103C-0490	Sigma Chemical Co. St. Louis, MO 63178
<u>Flavors</u>		
Aromalok Spearmint	761259	Fritzche DRG Inc. New York, NY 10011
Nat. Art. Peppermint Flavor, S.D.	120257	"
N.T. Art. Peppermint Citrus Flavor, Powder	120536	"

The fluidity of the formulation of the above identified Aberg application was increased by replacing a portion (50%) of the milled tribasic calcium phosphate with unmilled tribasic calcium phosphate.

Of all the formulations, the modified F-5 (87101) and modified F-6 (87102) were probably the best for both taste and flavor as well as tabletting properties.

The original formulation was not sweet enough nor was it flavored enough. Thus the rationale for modification.

The amounts of flavors, sweetner (Nutrasweet^{R}) and fluoride can be changed considerably without changing tabletting characteristics.

Nutrasweet^{R}	0-3%
Sodium Lauryl Sulphate	0-3%
Flavors	0-3%

The lubricant concentrations should not be changed radically. Lower amounts would not provide a sufficient degree of lubrication and higher quantities would reduce tablet hardness.

Mg. Stearate	1-1.5%
Stearic Acid	2-3%

The amount of xylitol could probably we doubled but sorbitol would then have to be decreased. Sorbitol could easily replace xylitol.

Glidant concentrations between 0.25 and 0.5% would be acceptable.

It would appear that the citric acid concentration could also be increased significantly which would increase foaming. However, excessive foaming would make a thin slurry rather than a paste, which is undesirable.

Citric Acid	4-10%

Changes of plus or minus 20% in Xanthan Gum would also probably not cause any tabletting problem.

The proportion of fillers and polishing agents should be greater than about 50% and the carbon dioxide couple less than about 35% by weight to insure that a paste rather than a slurry is formed; preferably greater than about 50% and

less than 25% respectively. If a zeolite is used the amount of carbon dioxide produced should be the same as in the couple percentages given.

Silicon dioxide and pyrogenic silica can be used as flow conditioning agents (in small quantities) as well as polishing agents.

The sugar fillers (sorbitol, mannitol, compressible sucrose, xylitol, fructose) can be interchanged in various proportions but such changes can change tablet hardness. Sugars can also be used to replace portions of polishing agents depending upon abrasiveness desired.

10-15% of microcrystalline cellulose will increase tablet hardness - without affecting other properties.

A small amount of disintegrating agent, may be added. The chewed particles will disintegrate faster and foam will generate faster. 1-2% of crospovidone or croscarmellose may be used.

The fluoride dentifrices accepted by the Council on Dental Therapeutics contain 0.1% fluoride ion. To achieve this level with sodium fluoride 0.22-0.24% is used; with sodium monofluorophosphate 0.76% is employed and with stannous fluoride, 0.4%. There are currently studies being conducted with 0.15% fluoride ion but these are not available at this time.

Over the counter fluoride rinses for daily use contain 0.05% sodium fluoride. This would be about 0.02% fluoride ion. The only comparable stannous fluoride product contains 0.1% stannous fluoride, which would yield about the same level of fluoride ion. There are also "once a week" fluoride rinses that contain 0.2% sodium fluoride (0.09% fluoride ion), but these are only available on a prescription basis.

All self-applied fluoride preparations have to be packed with no more than 120 milligrams of fluoride ion per container, the safety limit recommended by the Council on Dental Therapeutics.

The F-3 formula of the invention with 2.8 milligrams of stannous fluoride contains 0.7 milligrams of fluoride. The

recommended level for children above the age of three is 1 milligram per day. However, these are many situations in which higher levers are safely employed with the only concern some mild fluorosis. School water supplies are fluoridated at 4.5 PPM which would deliver 4 milligrams per day if a liter of water was consumed. Water supplies containing up to 3.5 parts per million naturally do not have to de-fluoridate. It would therefore appear that with a precaution "not to use below the age of six" (to avoid any possible fluorosis in the front teeth), 203 tablets, per day, delivering 1.4 to 2.1 milligrams of fluoride ion, would be acceptable.

Anti-plaque studies have employed from 0.1-0.4% stannous fluoride. Based upon these studies 0.4% stannous fluoride should exhibit an anti-plaque effect with continued use.

GENERAL METHOD OF MANUFACTURE FOR DENTAL TABLETS

1. Weigh out the xylitol, sorbitol, sodium lauryl sulfate, sodium bicarbonate and citric acid and pass through a #16 mesh security screen.
2. Weigh out the milled and unmilled tribasic calcium phosphate. Weigh out the sodium or stannous fluoride and Nutrasweet^{R} and make geometric dilution in two steps with a portion of the milled tribasic calcium phosphate.
3. Blend the sorbitol, xylitol, sodium bicarbonate, citric acid and xanthan gum in a V-blender for ten minutes.
4. Add the sodium lauryl sulfate to the mixture in (3) and blend for five minutes.
5. Add the sodium or stannous fluoride and Nutrasweet^{R}, triturate from (2), and the milled and unmilled tricalcium phosphate to the blend in (4) and blend for ten minutes.
6. Add the magnesium stearate and/or stearic acid and Cab-O-Sil^{R} and flavors to (5) and blend for five minutes.
7. Compress the finished blend on a Stokes RB-2 press with 7/16" flat-face tooling. Alternatively, slugging or roller compaction may be employed for granulation, particularly if particle size is very fine or the tablets are too soft.

Summary of In Vitro Studies

In vitro studies have been directed toward assessing the ability of tablets to deliver fluoride to teeth with the therapeutic goal of reducing dental caries. Studies have been designed in accordance with the guidelines adopted by the American Dental Association for the in vitro testing of dentifrices. Tests such as these are acceptable as in vitro indicators of fluoride therapy effectiveness.

The studies reported here are designed to monitor fluoride delivery performance in each of several situations that may occur in any one subject in vivo. The studies assess the following:

1. Release of fluoride from the tablet.
2. Uptake of fluoride by tooth enamel.
3. Remineralization of carious lesions.
4. Acid resistance of a remineralized lesion.

Each of these studies has been designed to simulate in vivo conditions the tablet might be exposed to. In the case of fluoride release, this means using synthetic salivas: one with a pH of 6.6 to mimic the resting saliva; the other with a pH of 4.5 to mimic the salivary composition during a caries attack. For the other studies, teeth were brushed with a slurry of the product. Brushing is a reasonable approximation to the enamel contact the tablets would encounter during chewing.

Summary of Fluoride Release Studies

This test measures the ability of the formulation to release fluoride into simulated saliva. Studies are done using water and also simulated salivas at pH 6.6 and 4.5 to simulate both resting saliva and the saliva composition after a meal.

Each tablet sample is suspended or mixed with test fluid amounting to 3 times the weight of the sample. If necessary, the mixture is centrifuged and the residual solid discarded. The fluoride concentration is determined in the supernatant liquid with a fluoride electrode.

Fluoride Release Results

Fluoride release from tablets into water and pH 4.5 and pH 6.6 synthetic salivas was measured. In each case the stannous fluoride tablets released more fluoride than did the sodium fluoride tablets. Release into either water of pH 6.6 synthetic saliva was about 45% of the total fluoride from the stannous fluoride preparation and on the order of 20-25% from sodium fluoride into synthetic saliva and 25-30% from sodium fluoride into water. Release from both tablets into the pH 4.5 synthetic saliva was somewhat less, with about 25% of total fluoride released from the stannous fluoride tablet and 20% from the sodium fluoride. In all cases the release kinetics were rapid, essentially reaching equilibrium within 120 seconds.

Summary of Fluoride Uptake Studies

This test is a measure of the ability of the product to cause fluoride incorporation into tooth enamel. Teeth mounted in a holder were exposed for 60 seconds to a slurry of the product in simulated saliva. This exposure is limited to a window of known area in each tooth. As a first approximation, total fluoride in each tooth can be determined by an acid etch procedure.

The procedure is as follows. The product sample is suspended or mixed with three times its weight of pH 4.5 synthetic saliva to form a slurry or solution. The mixture is agitated for 60 seconds and than a block of bovine enamel with a 0.25 cm^2 window is immersed in the slurry. After 5 minutes exposure to the mixture, the enamel is transferred to a vessel containing 10 ml of pH 6.6 synthetic saliva. After 6 hours exposure to this latter solution the sample is removed for analysis. The enamel window is exposed to 50 ul of a 0.5 M $HClO_4$ solution for 120 seconds. This exposure is repeated 2 additional times giving a total exposure time of 360 seconds. Each of these samples is then mixed with 5 ml of total ionic strength adjusting buffer (TISAB) and fluoride determined with the fluoride electrode.

Fluoride Uptake Results

Results were obtained for fluoride content in successive etches from teeth exposed to a slurry of either placebo or the stannous fluoride tablet for 60 seconds, followed by exposure to pH 6.6 synthetic saliva for 2 hours. In the first etched layer, (on the order of 20-50 microns depth) fluoride content was increased by a factor of 4.15; the second layer by 2.75 and the third by 2.88. Based on the usual fluoride content for bovine teeth of about 200 ppm fluoride, we estimate that we have delivered about 1000 ppm to the first layer and on the order of 500 ppm to deeper regions. This would be in the range of results we have obtained in a variety of solution fluoride delivery studies.

Summary of Remineralization Studies

This test measures the ability of the product to reverse the damage done to the enamel during a carious attack or series of such attacks. The in vitro testing procedure involves making an artificial lesion in a tooth, exposing this lesion to the product and then measuring the extent to which the lesion has been reversed. These effects are measured by using quantitative microradiography, a technique developed in our laboratory (see reprints) for application to dental studies. This technique can be used to measure the mineral content of the tooth as a function of position. Comparing the mineral content both before and after exposure to the product, we can quantitatively assess the extent to which the product has facilitated remineralization (reversal of the carious lesion).

The procedure is as follows. A 0.25 cm^2 enamel window is exposed to pH 4.5 synthetic saliva for 6 hours to produce an artificial lesion. The enamel is removed and half the window covered and the uncovered portion brushed for 2 minutes with an aqueous slurry of the product. This slurry is prepared by grinding the tablet for 60 seconds. After this brushing the sample is placed in pH 6.6 synthetic saliva for 24 hours. The enamel specimen is then removed and the min-

eral density profiles for the window exposed to product and the window subjected only to demineralization are determined. The difference in these two profiles is taken as the remineralization achieved during the 24 hour exposure. Triplicates of this test were done for brushing each of the products and the placebo product and also for a control exposed only to the synthetic salivas with no brushing.

Remineralization Results

Exposure to the placebo after demineralization does not lead to any measurable recovery of mineral. About 50% of the lost mineral was restored with a single exposure to the stannous fluoride tablet.

Summary of Acid Resistance Studies

After remineralization occurs, the tooth may have the same mineral content as does sound enamel. However, the resistance of this remineralized (repaired) lesion to subsequent acid attack is not necessarily the same as that of sound enamel. In this test the ability of a remineralized tooth to withstand a simulated acid attack is compared with that of sound enamel. Teeth that are remineralized with fluoride containing products often possess more acid resistance than does sound enamel. In other words, it can be more advantageous to have a lesion that has been repaired than to have sound enamel that has never had a lesion at all. Because of sensitivity problems with chemical assays, this test is most reliably accomplished by using the quantitative microradiography technique described above to assess mineral loss after the simulated attack.

The procedure is as follows. A window of enamel is exposed to pH 6.6 synthetic saliva for either 7 or 14 days. Three times during each day the enamel is removed and placed in pH 4.5 synthetic saliva for 60 minutes. After each such exposure, the enamel is brushed for 2 minutes with a 1:3 aqueous slurry of the product and then placed back in the pH 6.6 medium.

At the end of the treatment period, one half of the window is covered and the other exposed to the pH 4.5 synthetic saliva or to a 0.1 M pH 4.5 acetate buffer solution for 30, 60, 120, 240 or 480 minutes. During this exposure samples aliquots are taken at 4 predetermined spaced intervals and solution fluoride measured. The enamel is sectioned and mineral density profiles determined. The difference in total mineral content between the exposed and unexposed portions of the window is a measure of the demineralization that can occur after treatment with a given formulation. In this study, the stannous fluoride product, the placebo product and the absence of treatment were compared with respect to the relative amounts of enamel dissolved after treatment with each.

Acid Resistance Results

After the seven day treatment regimen using the stannous fluoride tablets, exposure of a tooth to pH 4.5 synthetic saliva for 4 hours led to erosion of between 20-30 microns of enamel. In contrast, an untreated tooth suffered complete erosion of about the first 80 microns of enamel.

ANTI-CARIES AND ANTI-PLAQUE ACTIVITY OF TABLETS CONTAINING STANNOUS FLUORIDE (SnF_2).

Rationale for the use of programmed feeding machine. Rodents (rats and hamsters) have been used extensively to estimate the cariostatic and plaque-reducing potential of a variety of agents. In many experiments care has not been taken to ensure that animals consumed the agent or that their frequency of eating has not been disturbed by the addition of the agent. To overcome these difficulties, which could have a significant effect on the incidence of dental caries or formation of dental plaque a Konig-Hofer programmed feeding machine has been employed in these studies. The programmed feeding machine permits the feeding of measured amounts of food at predetermined intervals. Animals are housed in individual cages which have a disk containing 18 small trays mounted in front. A measured amount of food is placed in the trays and the disk, rotated by means of a motor, presents each tray at the appropriate intervals. The test agent is placed in one or more trays and the remainder of the diet is placed in the remaining feeding trays. Alternatively the test agent may be mixed with one or more of the meals. Each tray is observed to ensure that the rat consumes the food and/or agent, and the amount of food consummed by each rat is determined by weighing the disk before and after a feeding cycle.

Purpose of the investigation

The purpose of the investigation was to determine whether the dentifrice tablet F-3 was capable of reducing the incidence of dental plaque and inhibiting the formation of dental plaque in rats when (a) incorporated in the food or (b) provided as a mouth rinse.

Experimental Design/Materials and Methods

A total of 50 Osborn-Mendel rats (19-21 days of age) were infected orally on days 19, 20 and 21 with the oral bacteria Streptococcus mutans strain

Ingbritt (serotype c) and Actinomyces viscosus T6. The rats were infected with these bacteria in order to promote the development of dental caries and dental plaque. Rats from each litter were equally divided into 5 groups of 10. This method of distribution of the rats was used to avoid "litter effect" influencing the outcome of the experiment.

The 5 groups were as follows:

Group 1 No Treatment

Group 2 F-3 rinse 3 times daily

Group 3 F-4 (placebo) rinse 3 times daily

Group 4 F-3 added to each meal

Group 5 F-4 (placebo) added to each meal

Preliminary studies indicated that the rats would not consume F-3 alone. A number of unsuccessful attempts were made to identify the component/s in the tablet that the rats found unpalatable. Therefore, it was decided to mix powdered F-3 into the basic diet. In order to overcome the possibility that the rats would show a preference for the meals that did not contain F-3 and avoid the F-3 containing meals, powdered F-3 was added to each meal at a concentration of 1 part F-3 to 50 parts food. As each meal tray contained 2g food the amount of F-3 was 1g ÷ 50 = 40 mg (0.18 mg SnF_2 or 0.044 mg F). As 17 meals were consummed each day the total daily intake of SnF_2 was 0.18 mg x 17 = 3.06 mg, while the total daily intake of F was 0.044 mg x 17 = 0.75 mg.

For the rinse a F-3 tablet was crushed and suspended in 2 ml water to form a slurry. A volume of 0.2 ml (0.28 mg SnF_2/0.059 mg F) was delivered into the mouth using a sterile 1 ml pipette 3 times daily. The total daily dose for each animal was 0.28 mg x 3 = 0.84 mg SnF_2 and 0.059 mg x 3 = 0.177 mg F. All animals were fed a cariogenic diet containing 28% sucrose. Deionized water was

available ad libitum. All rats were weighed weekly. The duration of the experiment was 35 days.

At the termination of the experiment the rats were killed and decapitated. The molar teeth were flooded with fluorescein to stain the dental plaque. The area of dental plaque covering the buccal and lingual/palatal surfaces of the teeth was recorded. The heads were then defleshed by autoclaving and smooth surface caries scored by the method of Keyes.

Results

The mean caries and plaque scores of the 5 groups of rats are shown in Tables 1 and 2. The purpose of the placebo groups was to determine whether components of F-3 other than the active agent (SnF_2) exhibit anti-plaque and/or anti-caries activity. It is clear that F-3 with SnF_2 exhibits significant cariostatic activity whether delivered as a rinse 3 times daily (66% reduction) or as an additive to the basal diet (77% reduction). Components of F-3 other than SnF_2 appear to contribute to its cariostatic activity because F-4 without SnF_2 affected a reduction in dental caries of between 27 and 35%.

Dental plaque inhibition (7-21%) was observed in rats receiving F-3 as a rinse and F-3 incorporated in the basal diet. The rinse was approximately three times more effective than the dietary addition in inhibiting plaque formation. The placebo tablet-fed rats formed more plaque than the untreated controls. Plaque reductions seen in the F-3 (SnF_2) vs. F-4 (placebo) were 35% for the rinse and 13% for the addition to the diet.

The magnitude of the reduction in dental caries and dental plaque observed in these experiments are clearly biologically significant. The reductions in dental caries are comparable to those obtained by optimal water fluoridation in the rat model. It should be noted that plaque inhibition has been observed in

the complete absence of mechanical cleansing. It is reasonable to anticipate that greater plaque inhibition would occur with the addition of mechanical cleansing.

Relevence of the experiments to the potential effectiveness of F-3 in humans

It is clearly difficult to extrapolate the results achieved in animals directly to humans, however, the rat model has proved a valid approach to predict the likely outcome of test agents in humans. The variable most likely to confound the extrapolation of rat data to humans, that of differences in eating frequency, has been eliminated by the use of the programmed feeding machine. The animal model employed in these experiments has already been shown to be capable of establishing differences in the cariogenic potential of human foods in an unequivocal and reproducible manner. In addition, the Council on Dental Therapeutics in its "guidelines for the acceptance of fluoride-containing dentifrices "(J.A.D.A., Vol. 110, April 1985, 545-547) accepts animal caries studies stating that..." the model is a good simulation of the effect of the fluoride dentifrice in humans".

Summary and Conclusions

F-3 dentifrice tablets containing stannous fluoride (SnF_2) were tested for their ability to reduce dental caries and dental plaque formation using a rat model incorporating programmed feeding. Identical F-4 tablets lacking SnF_2 served as placebos. The rats were fed a highly cariogenic diet and infected with caries and plaque inducing bacteria. F-3 containing SnF_2 significantly reduced the incidence of dental caries and inhibited the formation of dental plaque whether provided as a rinse or added to food. The placebo tablets also resulted in some caries but not plaque reduction.

Table V

Group		n	mean	Standard error of mean
1	No Treatment	10	12.4	2.9
2	Rinse with F-3 containing SnF_2	10	4.2	1.6
3	Rinse with F-4 without SnF_2 (placebo)	10	8.0	2.0
4	Food with F-3 containing SnF_2	10	2.8	0.8
5	Food with F-4 without SnF_2 (placebo)	10	9.0	2.2

Rank ordering low to high 4, 2, 3, 5, 1

- o F-3 (SnF_2) rinse: 66% reduction in caries compared with no treatment
- o F-3 (SnF_2) rinse: 48% reduction in caries compared with placebo
- o F-4 (placebo) rinse: 35% reduction in caries compared with no treatment
- o F-3 (SnF_2) in food: 77% reduction in caries compared with no treatment
- o F-3 (SnF_2) in food: 69% reduction in caries compared with placebo
- o F-4 (placebo) in food: 27% reduction in caries compared with no treatment

Table VI

Dental Plaque Scores (Smooth surfaces)

Group	n	mean	Standard error of mean
1 No Treatment	10	2.8	1.1
2 Rinse with F-3 containing SnF_2	10	2.2	0.3
3 Rinse with F-4 without SnF_2 (placebo)	10	3.4	0.8
4 Food with F-3 containing SnF_2	10	2.6	0.9
5 Food with F-4 without SnF_2 (placebo)	10	3.0	1.2

Rank ordering low to high 2, 4, 1, 5, 3

- o F-3 (SnF_2) rinse: 21% reduction in plaque compared with no treatment
- o F-3 (SnF_2) rinse: 35% reduction in plaque compared with placebo
- o F-4 (placebo) rinse: 21% more plaque compared with no treatment
- o F-3 (SnF_2) in food: 7% reduction in plaque compared with no treatment
- o F-3 (SnF_2) in food: 13% reduction in plaque compared with placebo
- o F-4 (placebo) in food: 15% more plaque compared with no treatment

It is obvious from the above data that stannous fluoride tablets (Formula F-3) have substantial anti-caries and anti-plaque activity. These data strongly support the view that these tablets are an effective anti-caries and anti-plaque agent in humans.

It will thus be seen that the objects set forth above, among those made apparent from the preceding description, are efficiently attained and, since certain changes may be made in carrying out the above method, the above articles and above compositions of matter without departing from the scope of the invention, it is intended that all matter contained in the above description shall be interpreted as illustrative and not in a limiting sense.

It is also to be understood that the following claims are intended to cover all of the generic and specific features of the invention herein described, and all statements of the scope of the invention which, as a matter of language, might be said to fall therebetween.

Particularly it is to be understood that in said claims, ingredients or compounds recited in the singular are intended to include compatible mixtures of such ingredients wherever the sense permits.

Having described our invention, what we claim as new and desire to secure by Letters Patent is:

1. A tooth cleaning and tooth fluoridating tablet forming a self-foaming paste when chewed in the mouth comprising:

A. less than about 50% by weight of a composition producing carbon dioxide when placed in the mouth;

B. greater than about 35% by weight of a substantially insoluble filling, and polishing composition; and a foam stabilizing, and wetting composition which together form a paste on chewing in the mouth; and,

C. an effective amount of stannous fluoride.

2. A tooth cleaning and tooth fluoridating tablet according to claim 1 wherein said filling, polishing, foam stabilizing, and wetting compositions comprise greater than about 50% by weight of said tablet.

3. A tooth cleaning and tooth fluoridating tablet according to claim 2 wherein said carbon dioxide producing composition comprises less than about 25% by weight of said tablet.

4. A tooth cleaning and tooth fluoridating tablet forming a self-foaming paste when chewed in the mouth comprising:

A. a composition producing carbon dioxide when chewed in the mouth;

B. a substantially insoluble filling and polishing composition; and a wetting and foam stabilizing composition which together form a paste on chewing in the mouth; and,

C. an effective amount of stannous fluoride.

5. A tooth cleaning and tooth fluoridating tablet according to claim 4 wherein said carbon dioxide producing composition comprises less than about 50% by weight of said tablet.

6. A tooth cleaning and tooth fluoridating tablet according to claim 4 wherein said insoluble filling and polishing composition comprises greater than about 35% by weight of said tablet.

7. A tooth cleaning and tooth fluoridating tablet according to claim 6 wherein said insoluble filling and polishing composition comprises greater than about 50% by weight of said tablet.

8. A tooth cleaning and tooth fluoridating tablet forming a self-foaming paste when chewed in the mouth comprising by weight:

A. about 65% of a polishing and filling composition;

B. about 18% of a carbon dioxide producing composition; and,

C. an effective amount of stannous fluoride.

9. A tooth cleaning and tooth fluoridating tablet according to claim 8 comprising by weight about 34% polishing agent and about 31% filling agent.

10. A tooth cleaning and tooth fluoridating tablet according to claim 8 comprising about 13% sodium bicarbonate and about 5% acid.

11. A tooth cleaning and tooth fluoridating tablet according to claim 8 and about 8.5% swelling agent.

12. A tooth cleaning and tooth fluoridating tablet according to claim 8 and about 1.5% wetting agent.

13. A tooth cleaning and tooth fluoridating tablet according to claim 9 comprising about 13% sodium bicarbonate and about 5% acid and

C. about 8.5% swelling agent; and,

D. about 1.5% wetting agent.

14. A tooth cleaning and tooth fluoridating tablet according to claim 13 and

E. about 10% lubricating agent.

15. A tooth cleaning and tooth fluoridating tablet according to claim 8 wherein said polishing agent is tri-calcium phosphate.

16. The method of tooth cleaning and fluoridating comprising:

A. placing a tablet according to claim 1 in the mouth;

B. chewing the tablet to form a self-foaming paste in the mouth;

C. swishing the paste around and through the interstices between the teeth to mechanically clean the teeth and bring tin and fluoride ions in contact with the tooth surfaces; and

D. swallowing the excess paste.

17. The method of claim 16 wherein said cleaning and swishing steps are carried out for at least one minute.

18. The method of claim 16 wherein said cleaning and swishing steps are carried out for at least two minutes.

19. The method of claim 16 wherein said steps are performed at least twice a day.

20. The method of tooth cleaning and fluoridating comprising:

A. placing a tablet comprising a carbon dioxide producing composition and a substantially insoluble filling and polishing composition and an effective amount of stannous fluoride in the mouth;

B. chewing the tablet to form a self-foaming paste in the mouth;

C. swishing the paste around and through the interstices between the teeth to mechanically clean the teeth and bring tin and fluoride ions in contact with the tooth surfaces; and

D. swallowing the excess paste.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US88/02098

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC(4): A61K 7/18 A61K 9/46 A61K 33/16

U.S.Cl.: 424/44 424/52 424/466

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
U.S.	424/44 424/52 424/466

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X	AU, A, 284579 (COVENTRY ET AL) 23 June 1966. (See the entire document).	1 to 15
Y	US, A, 3,431,339 (GYARMATHY ET AL) 4 March 1969. (See col. 6, lines 28 to 72).	16 to 20
A	DE, A, 2,051,499 (McNAMARA ET AL) 29 April 1971. (See the entire document).	1 to 15
X	US, A, 3,962,417 (HOWELL) 8 June 1976. (See col. 3, lines 1 to 44).	1 to 20
A	US, A, 4,157,386 (LaROCHELLE) 5 June 1979. (See the entire document).	16 to 20
A	US, A, 4,267,164 (YEH ET AL) 12 May 1981. (See the entire document).	1 to 15
A	G.B., A, 2,071,493A (YEH ET AL) 23 September 1981. (See the entire document).	1 to 15

[10] Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
25 AUGUST 1988	13 OCT 1988
International Searching Authority	**Signature of Authorized Officer**
ISA/US	Shep K. Rose SHEP K. ROSE

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

A	US, A, 4,308,252 (TOMAICH ET AL) 29 December 1981. (See the entire document).	1 to 15
Y	G.B., A, 2,163,348A (ABERG) 26 February 1986. (See the entire document).	1 to 20
T	US, A, 4,753,792 (ABERG) 28 June 1988. (See the entire document).	1 to 20

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers . , because they relate to subject matter [12] not required to be searched by this Authority, namely:

2. ☐ Claim numbers....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out [13], specifically:

3. ☐ Claim numbers_____, because they are dependent claims not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.